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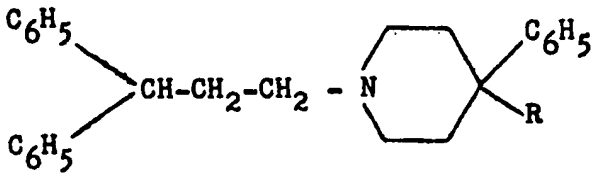
Piperidine derivatives bearing substituents in the 1 and 4 positions may be produced by reacting a piperidine derivative with a 1-halo-3,3-diphenyl-propane. These compounds are useful therapeutically as analgesics, anti-tussives and/or spasmolytics.

This invention relates to new piperidine derivatives bearing substituents in the 1 and 4 positions, their acid addition salts with mineral or organic pharmaceutically acceptable acids, their preparation and medicaments containing them.

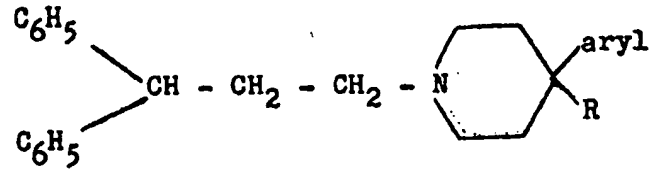
First the present invention provides compounds corresponding to formula I



(I)

in which R is hydroxyl or a group $-O-CO-R_1$, $-CH_2-OH$, $-CH_2-O-COR_1$ or $-CO-R_1$, R_1 being alkyl containing 1 to 4 carbon atoms.

The present invention furthermore provides compounds according to formula II



(II)

in which

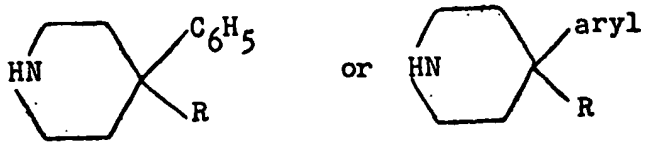
"aryl" is either phenyl or m-trifluoromethyl phenyl, and R means in the first case, $-CN$, $-CO-N(R_2)_2$ or $-O-CO-OR_1$ and in the second, $-OH$ or $-O-CO-R_1$,

R_1 represents, as indicated above, alkyl containing 1 to 4 carbon atoms and R_2 is H, CH_3 or C_2H_5 or $-N(R_2)_2$ represents a nitrogen heterocycle, particularly a pyrrolidine nucleus.

Of particular note are compounds in which R is CN, $CONH_2$, $OCOC_2H_5$ or CO-N⌐ while "aryl" is phenyl, and those in which R is OH or $OCOC_2H_5$ while "aryl" is m-trifluoromethyl phenyl,

as well as their hydrochlorides and maleates.

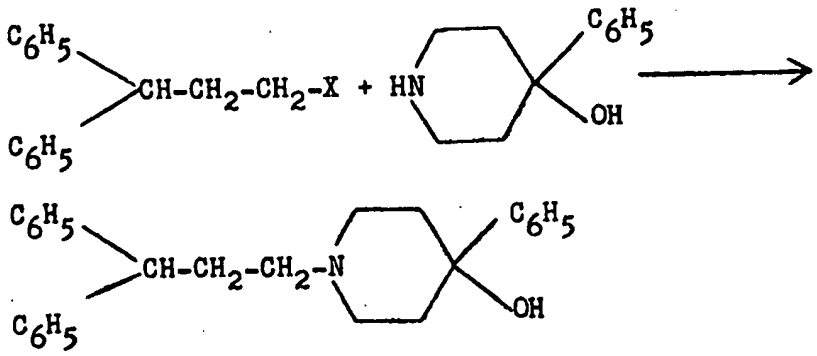
These compounds can be prepared principally by the reaction of a piperidine derivative corresponding to the formula



with a 1-halo-3,3-diphenyl propane, but numerous variants of this process are possible as indicated in the following reaction schemes, which are not limitative.

1) R_1 = OH

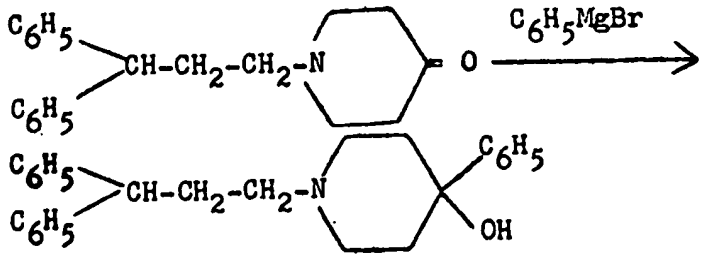
Scheme A



X = halogen, particularly bromine.

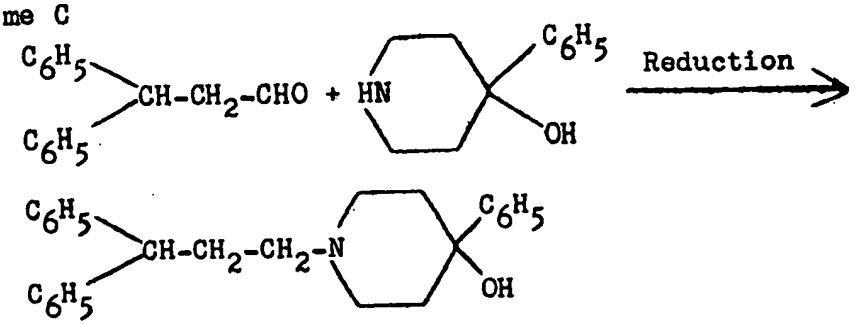
This reaction is preferably operated in the presence of a non-polar solvent such as toluene or other hydrocarbon, and a hydrohalic acid acceptor may be provided in the form of a tertiary base, pyridine or triethylamine for example.

Scheme B



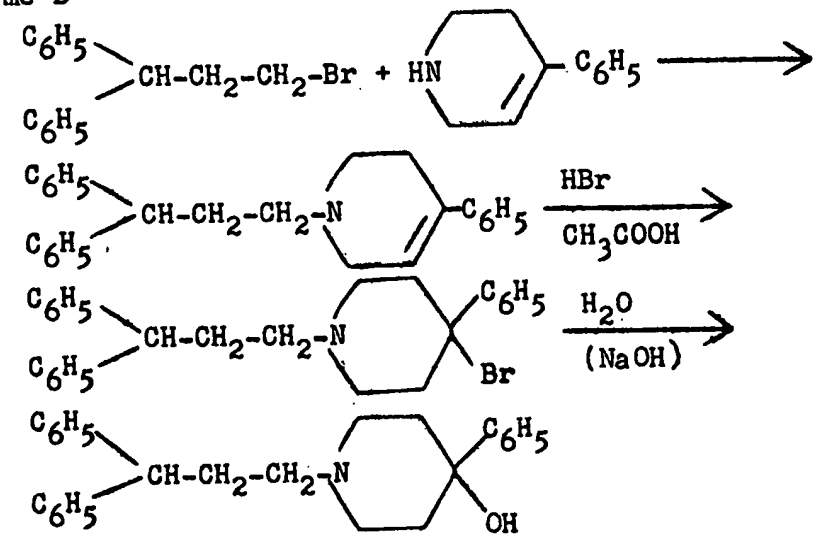
The Grignard reaction takes place in the usual conditions in solution in preferably ether or tetrahydrofuran.

Scheme C



The reduction is preferably effected catalytically by hydrogen in the presence of palladium on charcoal in an alcoholic solvent such as methanol.

Scheme D

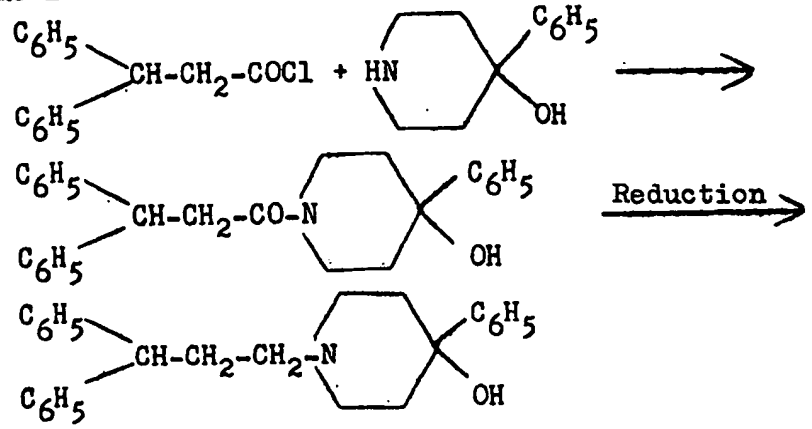


The first stage of this synthesis is carried out in conditions similar to those indicated above for Scheme A.

The bromination is preferably effected in acid conditions and the hydrolysis in an alkali medium.

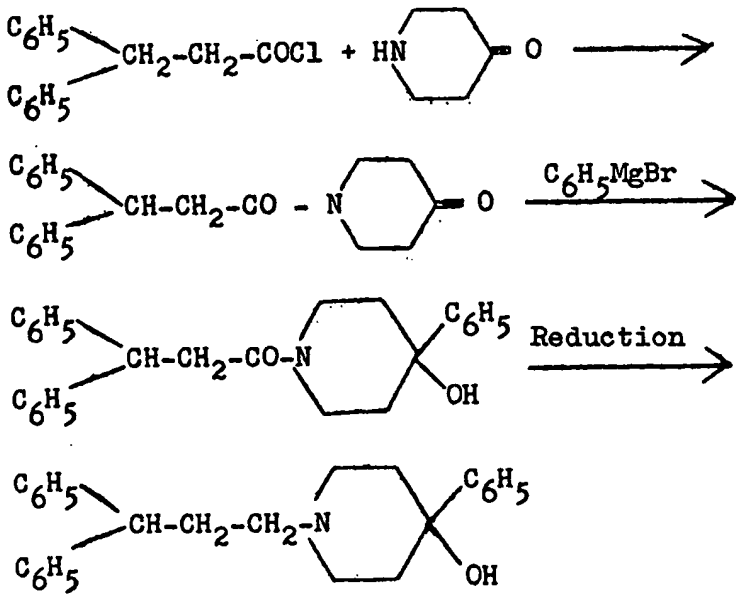
In general the brominated intermediate is not isolated.

Scheme E



Here the reduction may be catalytic or chemical, the method of choice consisting in using lithium aluminium hybride in the usual conditions.

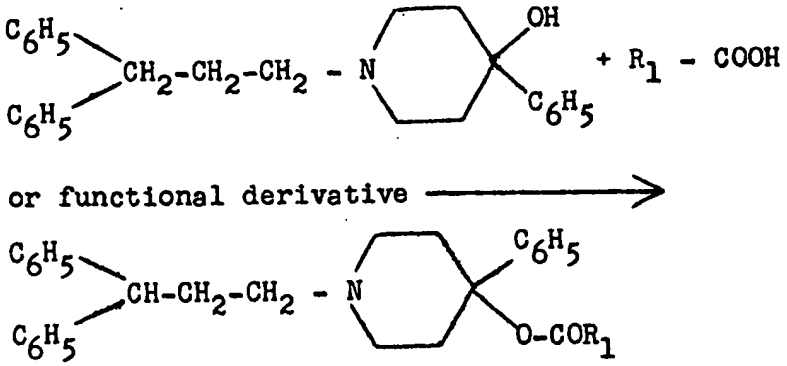
Scheme F



The preparation of the amide and the Grignard reaction are carried out in the usual way, while the reduction is advantageously carried out in conditions mentioned for Scheme E.

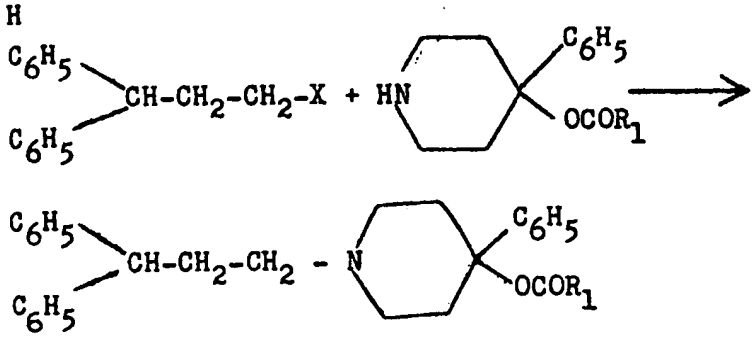
2) R = O-COR$_1$

Scheme G

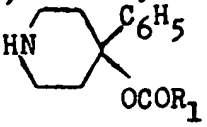


The starting alcohol is prepared according to any of Schemes A to F. The functional derivative of the acid is particular an anhydride or a halide, notably the chloride, and the reaction is carried out in the warm in a non-polar solvent such as chloroform.

Scheme H

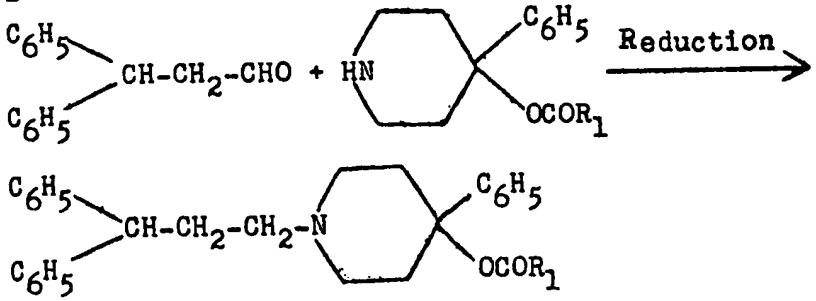


X = halogen, notably bromine.

The esters  being unstable,

must be prepared in situ by the reaction of the 4-phenyl-4-piperidinol and a functional derivative of the desired aliphatic acid (particularly the chloride) and then allowed to react immediately with the 3,3-diphenylpropyl halide.

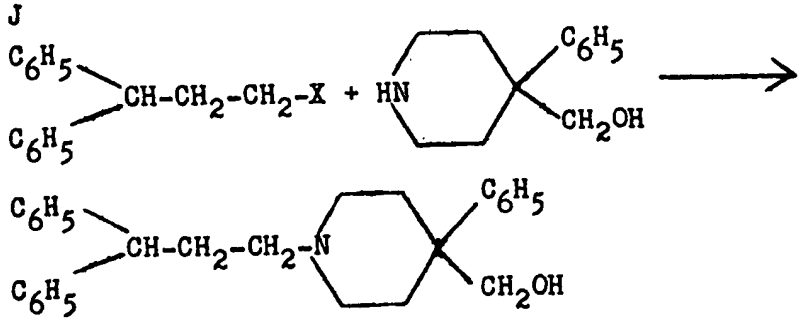
Scheme I



The reaction is a variant of that described under Scheme C and is carried out in similar fashion, taking the precautions noted under H.

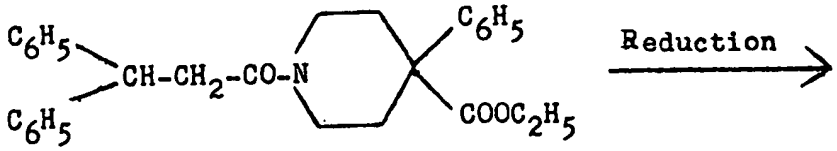
3) R = $-CH_2OH$

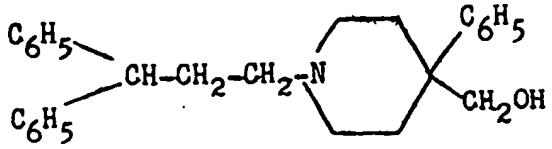
Scheme J



This reaction is carried out in the usual conditions (cf Schemes, A, D and H).

Scheme K

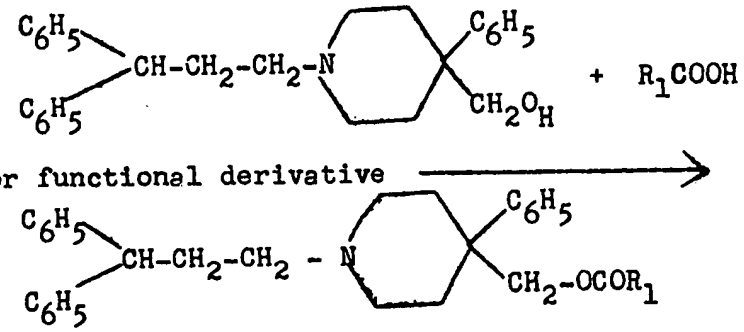




The reductions of the two carbonyl groups are effected simultaneously, either catalytically or chemically, particularly with the aid of lithium aluminium hybride in a non-polar solvent medium such as tetrahydrofuran.

4) R = $-CH_2-O-COR_1$

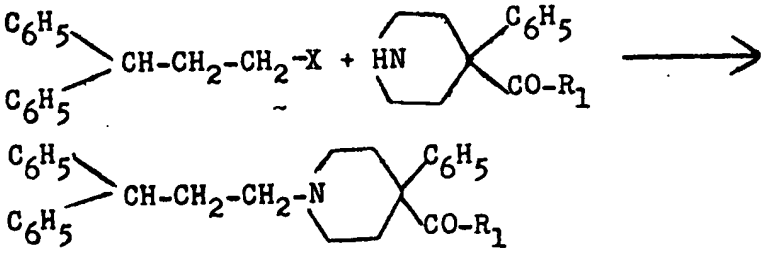
Scheme L



The starting product is obtained according to Schemes J or K and the final reaction is carried out in a fashion similar to that described under G.

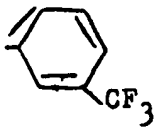
5) R = COR_1

Scheme M

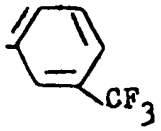


X = halogen, notably bromine.

The reaction is carried out preferably in a non-polar solvent medium, for example chloroform, in the presence of a hydrohalic acid acceptor base and at the boiling temperature.

6) R = OH and aryl = 

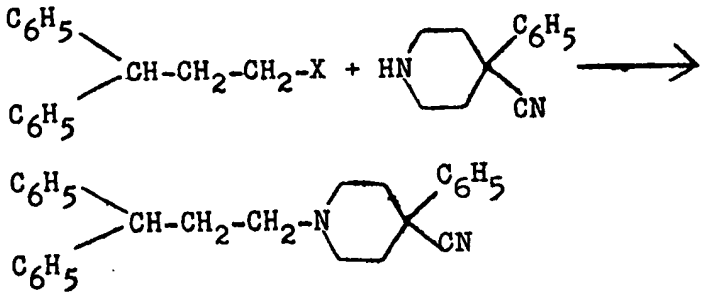
schemes A, B, C, D, E, F above.

7) R = O - CO - R_1 and aryl = 

schemes G and H above.

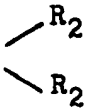
8) R = -CN and aryl = $-C_6H_5$

scheme N

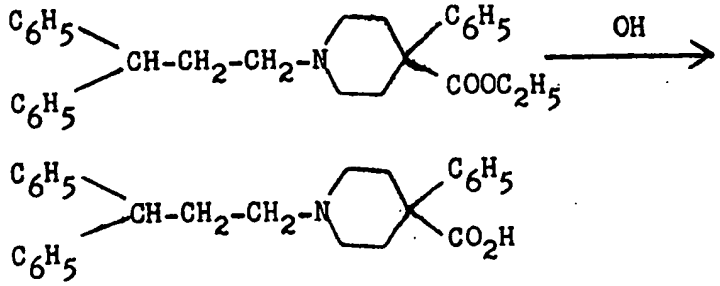


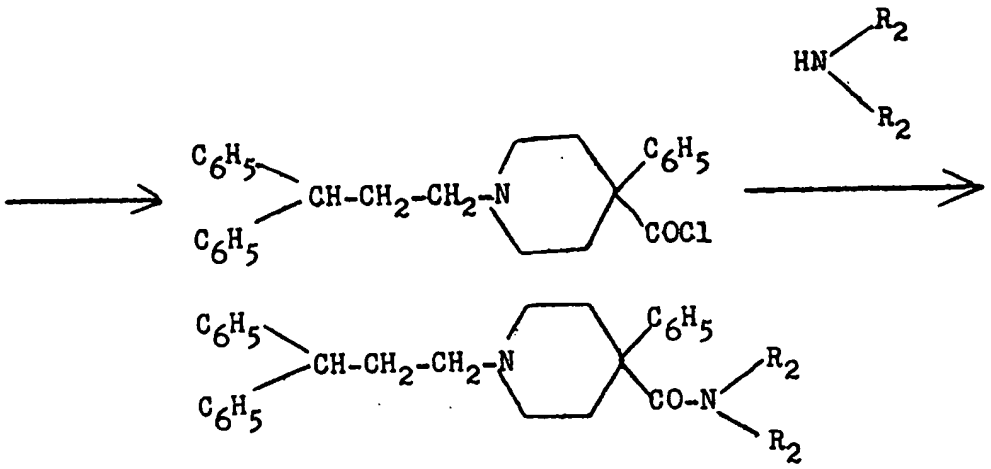
X = halogen, notably bromine.

The reaction is then conducted preferably in a non-polar diluent such as chloroform in the presence of a hydrohalic acid acceptor base and at the reflux temperature.

9) R =  and aryl = $-C_6H_5$

Scheme O

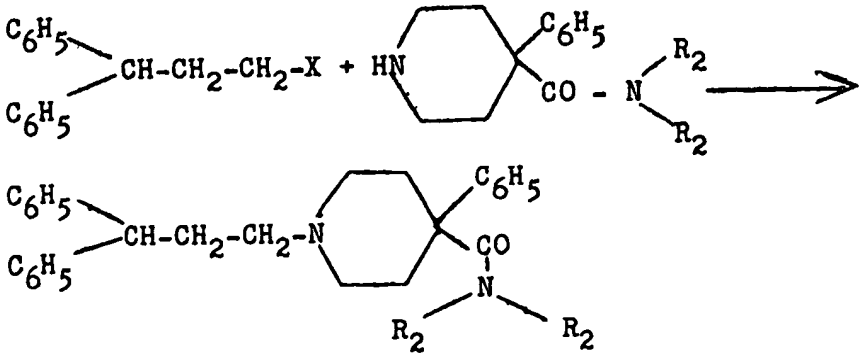




The free acid may be obtained by alkaline saponification of the ester ; the chloride of the acid may be prepared by the classical methods of obtaining compounds of this type, the synthesis of choice being that of reaction of oxalyl chloride with the acid in the body of a non-polar diluent such as chloroform

The transformation of the chloride of the acid (or of the ester) into the amide can be carried out by reaction of an secondary amine or if R_2 = H of ammonia, in the presence of a polar diluent such as water or a non-polar diluent, particularly chloroform, or without solvent.

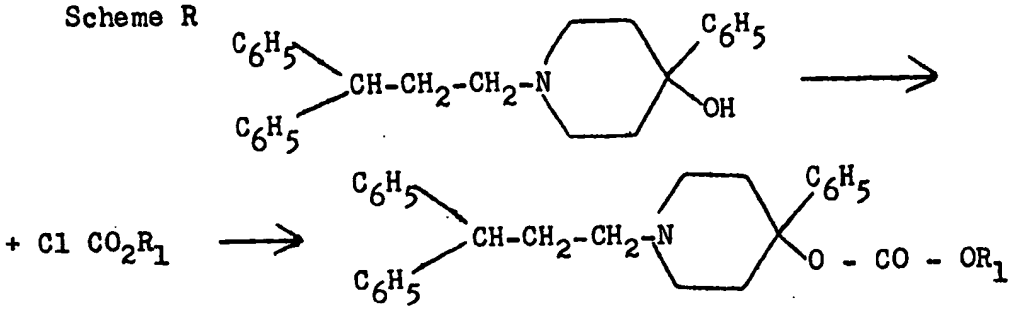
Scheme P



This reaction is carried out in conditions similar to those which are described above for Scheme N.

10) R = -O-CO-OR_1 and aryl = C_6H_5

Scheme R



The reaction is carried out preferably at the boiling temperature of a non-polar diluent, for example chloroform, in the presence or in the absence of a hydrohalic acid acceptor base.

The products of the invention can be used in human and veterinary therapy, notably as analgesics, anti-tussives and/or spasmolytics.

The following non limitative examples will show further how the invention may be put into practice.

EXAMPLE 1 :

1-(3,3-diphenyl-1-propyl)-4-phenyl-4-piperidinol (R = OH) (code number 70-264 R and C)

Preparation according to Scheme A.

4-phenyl-4-piperidinol is a known product which can be prepared according to any of the methods described in the literature, particularly according to that of Mac Elvain and McMahon, J. Am. Chem. Soc. 1949, 71, 901.

Into a three-neck flask provided with stirrer, dropping funnel and reflux condenser are introduced 22.0 g (0.12 mol) of 4-phenyl-4-piperidinol and 200 ml of toluene.

The mixture is kept on the reflux until complete solubilization and there is then added dropwise a solution of 19.4 g (0.07 mol) 1-bromo-3,3-diphenyl-propane in 50 ml toluene, over about one hour. The mixture is refluxed for 20 hours.

After cooling, the hydrobromide of 4-phenyl-4-piperidinol is filtered and washed with ether. The filtrate and the washing liquids are combined and evaporated. The crystalline product is taken up in ether, the solution is filtered and re-evaporated. The compound 70-264 R and C is recrystallised in hexane.

Yield 14.7 g, i.e. 66%

Melting point 106-107°.

The hydrochloride is prepared with the dry hydrochloric acid in solution in ether.

Melting point 260°.

Analysis : mineral Cl (%) calculated 8.71
found 8.75

EXAMPLE 2 :

1-(3,3-diphenyl-1-propyl)-4-phenyl-4-piperidinol (R = OH) (code number 70-264 R and C)

Preparation according to Scheme C.

In the presence of palladium on charcoal a solution of 21g (0.1 mol) of 3,3-diphenylpropionaldehyde and 17.7 g (0.1 mol) of 4-phenyl-4-piperidinol in 200 ml of methanol is hydrogenated. When the absorption has ceased, the catalyst is filtered and the solution evaporated into dryness under reduced pressure. The residue is taken up in ether. By passing through gaseous hydrochloric acid the hydrochloride of the desired product is obtained which is washed with water to eliminate the hydrochloride

of unreacted 4-phenyl-4-piperidinol.

The salt is recrystallised in a mixture of alcohol and ether. 24,8 g of product are obtained melting at 260° i.e. a yield of 61%.

Analysis : mineral Cl (%) calculated 8.71
found 8.73

EXAMPLE 3 :

1-(3,3-diphenyl-1-propyl)-4-phenyl-4-piperidinol (R = OH) (code number 70-264 R and C)

Preparation according to Scheme D.

The 4-phenyl-1,2,3,6-tetrahydro pyridine can be prepared according to a method described in the literature, and in particular that of Schmidle and Mansfield, J. Am. Chem. Soc. 1956, 78, 1702.

In a 500 ml Erlenmeyer flask provided with a reflux condenser a dropping funnel and a magnetic stirrer there was dissolved 23.4 g (0.147 mol) of 4-phenyl-1,2,3,6-tétrahydro pyridine in 150 ml of toluene with few crystals of sodium iodide. The mixture was brought to reflux and there was added dropwise a solution of 20.2g (0.0735 mol) of 1-bromo-3,3-diphenyl propane in 100 ml of the same solvent. The mixture was refluxed for 15 hours. The precipitated hydrobromide of 4-phenyl-1,2,3,6-tetrahydropyridine was filtered and washed with ether. The toluene was evaporated. The residue was taken up by ether and the separated organic layer was washed with water, dried and concentrated under reduced pressure.

On cooling, 16.3g of 1-(3,3-diphenyl-1-propyl)-4-phenyl-1,2,3,6-tetrahydropyridine crystallised, i.e. a yield of 63%. Its melting point was 104°. The hydrochloride (prepared in isopropanol and precipitated by ether) melts at 185°.

Analysis : amine dosage : equivalent

calculated 353
found 354

A solution of this intermediate (in free form) (17.6g = 0.05 mol) in 200 ml glacial acetic acid is saturated with gaseous hydrobromic acid for 2 hours at 15°. The mixture was left to stand overnight, the precipitate filtered and stirred for half-an-hour in a vapour bath of aqueous ethanol. After cooling, the mixture was alkalinized with an excess of a solution 10N of sodium hydroxide. The precipitate obtained after evaporation of the alcohol is filtered and recrystallised in hexane. Yield is 7.4 g i.e. 40%. Melting point is 106°.

The product was transformed into the hydrochloride (cf. examples 1 and 2) this salt melts at 260°.

Analysis : mineral Cl (%) calculated 8.71
found 8.70

EXAMPLE 4 :

1-(3,3-diphenyl-1-propyl)-4-phenyl-4-propionyloxy piperidine ($R = -O-COC_2H_5$) (code number 70-285 R and C)

Preparating according to Scheme G.

In an Erlenmeyer flask, provided with a reflux condenser, a dropping funnel and a magnetic stirrer there were dissolved 3.7 g (0.1 mol) of 1-(3,3-diphenyl-1-propyl)-4-phenyl-4-piperidinol in 100 ml chloroform and the mixture brought to boiling point. There was then introduced dropwise 1.20 g (0.013 mol) propionyl chloride. It was noted on the course of the addition that very substantial temperature increase took place. The mixture was heated under reflux for 4 hours. There were then added again 0.3 ml propionyl chloride and the mixture heated for one hour

at 70°, The mixture was left to stand for 2 days and the mixture then evaporated almost to dryness. By trituration of the residue in petroleum ether, the products crystallised. The product was taken up in alcohol, the solution acidified with gaseous hydrochloric acid and evaporated to dryness. After recrystallisation in isopropanol, 2.8g of the hydrochloride of compound 70-285 R and C was obtained, i.e. a yield of 60%.

Melting point : 190°

Analysis : mineral Cl (%) calculated 7.6.
found 7.6

EXAMPLE 5 :

1-(3,3-diphenyl-1-propyl)-4-phenyl-4-hydroxymethyl piperidine ($R = CH_2OH$) (code number 70-263 R and C)

Preparation according to Scheme J.

The 4-phenyl-4-hydroxymethyl piperidine is already described in the literature but an improved preparation of this compound has been discovered, which is described below.

To a solution of 1g (0.0263 mol) lithium aluminium hydride in 100 ml ether there was added dropwise a solution of 2.33g (0.01 mol) of 4-phenyl-4-ethoxycarbonyl piperidine (prepared in particular according to Eisleb, Berichte 1941, 74B, 1433) in 20 ml of the same solvent. The mixture was then kept at reflux for 2 hours and then left standing overnight and hydrolysed with a 10% solution of sodium potassium tartrate. The solid obtained is filtered and taken up in hot benzene or cold chloroform. The mixture is filtered again and the filtrate evaporated.

1.2 g of a fine white solid were obtained as the evaporation residue.

Yield : 63 %

Melting point 172° after recrystallisation in a benzene isopropanol mixture.

Analysis : amine dosage : Equivalent

calculated 191.3
found 193.4

The hydrochloride is prepared by addition of a solution of gaseous hydrochloric acid in ethanol to a solution of the base in the same solvent. The salt is precipitated by a large quantity of ether.

Melting point 264° after crystallisation in isopropanol containing a little ethanol.

The condensation of the 4-phenyl-4-hydroxymethyl piperidine with the 1-bromo-3,3-diphenylpropane takes place in conditions similar to those which have been described in Examples 1, 3 and 7.

The compound 70-263 R and C is a very viscous oil of glassy appearance which boils at 210-215°/0.04 mm. It is obtained in yield of 62%.

Analysis : amine dosage (equivalent)

calculated 385
found 387.

The hydrochloride obtained by dissolving the base in ether and the addition of anhydrous hydrochloric acid in solution of the same solvent until a clearly acid pH. It is a white powder which is washed with ether and dried in an oven.

Melting point 158°

Analysis : mineral Cl (%) calculated 8.42
found 8.47

EXAMPLE 6 :

1-(3,3-diphenyl-1-propyl)-4-phenyl-4-hydroxymethyl piperidine ($R = CH_2OH$) (code number 70-263 R and C)

Preparation according to Scheme K.

The 1-(3,3-diphenylpropionyl)-4-phenyl-4-ethoxycarbonylpiperidine starting material is prepared by reaction of 4-phenyl-4-ethoxycarbonylpiperidine (cf. Example 5) with 3,3-diphenylpropionyl chloride.

To a stirred solution of 7g (0.03 mol) of 4-phenyl-4 ethoxycarbonylpiperidine in 100 ml toluene is added at about -5° a solution of 3.7g (0.015 mol) of 3,3-diphenylpropionyl chloride in 15 ml of the same solvent. The mixture is allowed to come back to ambient temperature and reaction ended by heating for half an hour at 50°.

The toluene solution obtained is concentrated to dryness under reduced pressure ; the residue is taken up in ether, then by water in order to eliminate the amine hydrochloride. The portion insoluble in water and ether is dried in an oven and recrystallised in isopropanol.

5.9g of the intermediate compound are obtained, i.e. a yield of 91%.

Melting point : 150°

Analysis : N (%) calculated 3.18
found 3.20.

To a stirred suspension of 0.74 g (0.02 mol) lithium aluminium hydride in a 150 ml of anhydrous tetrahydrofuran are added, under a nitrogen atmosphere, 4.4 g (0.01 mol) of the preceding product in solution in 100 ml of the same solvent. After 4 hours refluxing the reaction mixture is cooled and hydrolysed with an aqueous 20% solution of sodium potassium tartrate.

When the reaction is ended the precipitate is filtered washed with ether and the filtrates are concentrated to dryness. The residue is fractionated.

3.1 g of compound 70-263 R and C are obtained i.e. a yield of 80%.

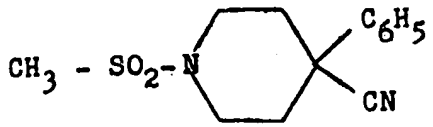
Boiling point 210 - 215°/0.04 mm
Analysis : amine dosage : equivalent
calculated 385
found 389

EXAMPLE 7 :

1-(3,3-diphenyl-1-propyl)-4-phenyl-4-propionyl piperidine ($R = COC_2H_5$) (code number 70-286 R and C)

Preparating according to Scheme M.

The 4-phenyl-4-propionyl piperidine starting material is a product described in the literature. It can be prepared in particular by the methods of Eisleb, Berichte 1941, 74 B, 1433 (which describes the first material



), of McFarlan and Co. Ltd. British Patent Specification 841120 or of Boggiano et coll. J. Chem. Soc. 1959, 1143-50. The hydrochloride of this compound melts at 208°.

2.17 g (0.01 mol) of the base is introduced into a grinded Erlenmeyer flask provided with a magnetic stirrer and there is added 1.01g (0.01 mol) of triethylamine and 40 ml of chloroform. The mixture is cooled in a bath of ice and there is added dropwise in half an hour 2.75g (0.01 mol) of 1-bromo-3.3-diphenylpropane dissolved in 15 ml of $CHCl_3$. The mixture

is heated for 15 hours under reflux.

After evaporation of the solvent until dryness, the residue is taken up in ether in order to precipitate the triethylamine hydrobromide formed (1.6g thereof are obtained ; theoretical quantity 1.82g). The ether of the filtrate is evaporated and 3.71g i.e. a yield of 90%, of compound 70-286 R and C are obtained in the form of a light brown oil, the purity of which is verified by thin layer chromatography, the eluent being a mixture of acetone and methanol (50:50).

1.2g maleic acid are dissolved in 50 ml isopropanol and there is added thereto, progressively and with stirring, 3.4g of the oily base previously obtained and dissolved in 50 ml of isopropanol. The maleate precipitates at the end of a short while. An excess of ether is added, the salt filtered, washed with isopropanol and then with ether and then dried in an oven.

2g are obtained, i.e. a yield of about 50%

Melting point : 159°

Analysis : amine dosage : equivalent calculated 527
found 526

EXAMPLE 8 :

1-(3,3-diphenylpropyl)-4-phenyl-4-cyanopiperidine (or 1-(3,3-diphenylpropyl)-4-phenyl-4-piperidyl) carbonitrile) and its hydrochloride (II, R = CN, aryl = C_6H_5) (code number 70-308 R and C ; preparating according to Scheme N).

In a 250 ml Erlenmeyer flask provided with a magnetic stirrer there are introduced 0.96 g sodium (0.04 mol) in a 100 ml ethanol.

When all the metal is dissolved there is added in portions 9.1g (0.04 mol) of the hydrochloride of 4-phenyl-4-piperidino nitrile (or hydrochloride of (4-phenyl-4-

piperidyl) carbonitrile) (prepared according to KWARTHER and LUCASJACS 1947, 69, 2582). The mixture is stirred for an hour, evaporated to dryness and ether added which precipitates the sodium chloride and this is filtered off. The ethereal solution is evaporated to dryness. The residue is taken up in 50 ml chloroform and there is added 4.04g of triethylamine in 35 ml chloroform. This solution is cooled by an ice bath and there is then added dropwise in about one half an hour 11 g (0.04 mol) 3,3-diphenylpropyl bromide dissolved in 60 ml of the same solvent. The mixture is heated for 8 hours under reflux and then left two days standing. The chloroform is evaporated, the residue taken up by ether and the triethylamine hydrobromide formed filtered off. After drying the ethereal phase, it is acidified by hydrochloric acid in a solution in ether. 7.5g of a white precipitate are obtained. Thin layer chromatography (eluent : acetone/methanol, 75/25 ; developer iodine) having shown that the product obtained was contaminated with starting piperidine, the impure compound was taken up in 50 ml water, the insoluble part filtered off, dried in an oven and recrystallised in isopropanol. 4.4g of the desired hydrochloride were obtained, i.e. a yield of 26%, explained by the weak solubility of this body in water. The yield may be improved by using 2 molecules of amine per 1 molecule of 3,3-diphenylpropyl bromide.

Analysis : ionised Cl calculated % 8.52

found % 8.56

The salt melts at 222°, its solubility in water is less than 10^{-4}%.

EXAMPLE 9 :

1-(3,3-diphenylpropyl)4-ethoxycarbonyloxy-4-phenylpiperidine and its hydrochloride (II, R = O-CO-OC_2H_5 and aryl = C_6H_5 (code number 71-119 R and C ; preparation according to Scheme R).

In a grinded Erlenmeyer flask of 250 ml capacity provided with a reflux condenser and with a calcium chloride guard tube for protection against humidity there was introduced 9.7g (0.025mol) of 1-(3,3-diphenylpropyl)-4-phenyl-4-piperidinol, and 3 g (0.098 mol) ethylchloroformate dissolved in 150 ml anhydrous chloroform, and the mixture was brought to reflux for 25 hours. The solvent was then evaporated, and the residue taken up by ethanol and the base transformed into the hydrochloride by the passage of gaseous hydrochloric acid. The alcohol is evaporated ; the residue, an amorphous powder, is crystallised by dissolving in the minimal quantity of isopropanol, addition of 500 ml ether and standing overnight in a refrigerator. 7.9g of the desired salt are obtained, well crystallised, i.e. a yield of 66.66%.

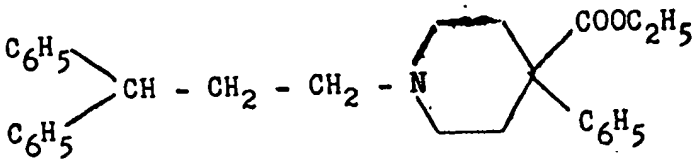
Analysis : ionised Cl : calculated % 7.40
found % 7.33.

The product melts at 122°. Its solubility in water is about 5 x 10^{-4}%, the pH of the saturated solution being equal to 5.

EXAMPLE 10 :

1-(3,3-diphenylpropyl)-4-phenyl-4-pyrrolidino carboxamido piperidine and its maleate (II, R = -CO-N◻ , aryl = C_6H_5). (code number 71-206 R and C ; preparating according to Scheme O).

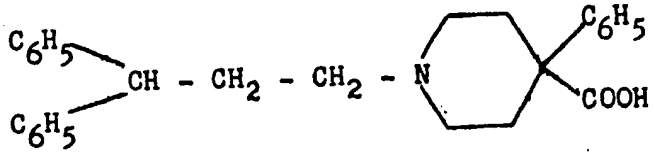
The starting 4-ethyl carboxylate of 4-phenyl piperidine is prepared according to the method of Eisleb Berichte 1941, 74B, 1435, modified by Thorp and Walter J.C.S. 1948, 559 and Dalkhom Acta Chem. Scand. 1963, 17, 227 ·By reaction of this product with 3,3-diphenylpropylbromide in chloroform and under reflux, the 1-(3,3-diphenylpropyl)-4-phenyl piperidine-4-ethyl carboxylate of formula



is obtained, which has not been purified.

4g (0.1 mol) of caustic soda are dissolved in a just sufficient quantity of ethanol and then in the cold there is added 10.7g (0.025 mol) of the above ester, dissolved in the minimum of the same solvent. After 4 hours refluxing, the saponification is ended.

The alcohol is evaporated and the residual solids taken up by mixture of water and ether ; the phases are decanted, the organic layer separated and washed. The aqueous phases are acidified ; a gum precipitates which crystallises rapidly and a fine beige solid which is extracted, washed with water then with isopropanol and then with ether. There can thus be obtained 9g of the hydrochloride of 1-(3,3-diphenylpropyl)-4-phenylpiperidine-4-carboxylic acid



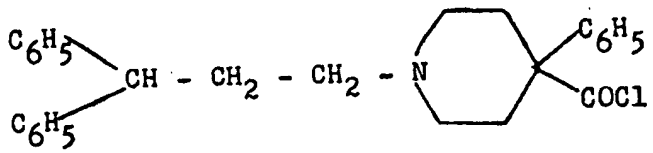
i.e. a yield of 82.5%. This salt melts at 258°.

Analysis : ionised Cl calculated % 8.15
found % 8.07

6.4g (0.0147 mol) of this material are placed in suspension in a 150 mol anhydrous chloroform and then this is cooled by an ice bath. There is poured dropwise into the mixture 15 ml oxalyl chloride. The mixture is allowed slowly

to revert to ambient temperature and it is then placed for 30 hours under reflux. 5 ml oxalyl chloride are added and the mixture further heated for 20 hours at boiling.

The mixture is evaporated to dryness. The resulting oily solid is taken up by a mixture or ether and acetone and totally solidified by trituration. It is extracted, washed and dried. The hydrochloride of the acid chloride is obtained



HCl in the form of a fine white solid.

Yield : 52.5% (3.5g)

Analysis : total Cl : calculated % 15.65
found % 15.67

In a solution, cooled in ice, of 3 ml redistilled pyrrolidine in 30 ml anhydrous chloroform, is introduced dropwise a solution of 1.5 g (0.0033 mol) of the hydrochloride of the preceding acid chloride in 30 ml of the same solvent. The mixture was heated for two days under reflux. The chloroform was evaporated and the residue taken up in a mixture of water, ether and benzene. After filtration, the aqueous phase is decanted, the organic phase is washed with water and then dried and evaporated.

The residue is taken up in ethanol, 1g of sodium hydroxide and a few drops of water added and the mixture left for about 24 hours standing at ambient temperature. The mixture is then filtered to remove the brown impurities ; the filtrate is evaporated to dryness and the residue is again taken up in a mixture of water, ether and benzene. The organic phase is

decanted, washed, dried and again concentrated once.

A pale yellow oil is obtained which may be crystallised to give a white solid by trituration with ether and petroleum ether. The amide is extracted, washed and dried.

1g of fine crystals of the product are collected, i.e. a yield of 67% ; it melts at 127° and its purity is demonstrated by thin layer chromatography.

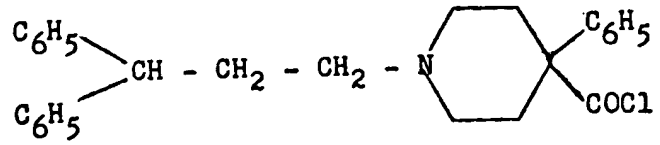
Analysis : dosage of amine function M calculated 452.5
M found 455.8

The maleate of this amine can be prepared in the following way. In ethanol, 1.6g of the base are mixed with 408 mg of maleic acid, the mixture filtered and the limpid solution obtained evaporated to dryness. A white crystalline solid is obtained ; this is taken up in ether, pulverized, extracted, washed with ether and dried. 1.95 g of the salt are obtained, i.e. a yield of 97.5%. The product melts at 183°. Its solubility in water is 2.5×10^{-4}%, the pH of a saturated solution being 5.1.

EXAMPLE 11 :

1-(3,3-diphenylpropyl)-4-phenyl-4-carboxamido piperidine and its hydrochloride (II, R = $-CONH_2$, aryl = C_6H_5) (Code number 71-254 R and C ; preparation according to Scheme 0).

Into 150 ml of concentrated ammonia, cooled to 2°, there is introduced very rapidly with the aid of a spatula 4.7 g (0.01035 mol) of the hydrochloride of the acid chloride



prepared according to example 10. Vigorous stirring is carried out for 2 days, the mixture heating itself up spontaneously.

The white solid is filtered, strongly pressed and carefully washed with water before drying. It is then dissolved in acetone, with stirring and a small quantity of insoluble impurity is eliminated by filtration. The solution is treated with animal charcoal filtered and evaporated to dryness. An oil results which can be crystallised with some difficulty in a mixture of cyclohexane and benzene. The yield is 85%. The product melts at 127°.

Analysis : Dosage of amine function M calculated 398
M found 399.

The purity is demonstrated by thin layer chromatography.

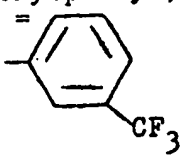
The hydrochloride of the amide is prepared in the following way : the crude base is dissolved in a mixture of acetone and ether and then there is introduced thereto dropwise a solution of hydrochloric acid in ether until a very distinctly acid pH ; the precipitate is extracted, washed several times with ether and dried in an oven.

4g of the salt are obtained, i.e. a yield of 89%. This hydrochloride melts at 252°. Its solubility in water is less than 1×10^{-4}%.

Analysis : Ionised Cl calculated % 8.17
found % 8.14.

EXAMPLE 12 :

1-(3,3-diphenylpropyl)-4-(3,trifluoromethylphenyl)-4-piperidinol and its hydrochloride (II, R = OH, aryl =



(code number 71-276 R and C ; preparation according to Scheme A).

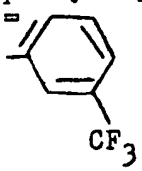
In a polished 250 ml flask provided with a reflux condenser and a dropping funnel are introduced 7.37g (0.0301 mol) of 4-(3,trifluoromethylphenyl)-4-piperidonal, 5g of sodium carbonate, 125 ml of methylisobutyl ketone and a few crystals of sodium iodide. The mixture is heated to 80° and there is then added dropwise 8.3g (0.0301 mol) of 3,3-diphenylpropyl-bromide, dissolved in 30 ml of methylisobutyl ketone. The mixture is heated for 4 days under reflux. After evaporation of the solvent the residue is taken up in a mixture of other and water. The organic phase is decanted, washed with water and dried over magnesium sulphate.

The hydrochloride of the piperidinol is obtained by adding hydrochloric acid dissolved in ether to the dried preceding solution. 12 g of the salt are obtained, i.e. a yield of 83.8%.

The product melts at 185°. Its solubility in water is less than 1×10^{-4}% .

Analysis : Ionised Cl calculated % 7.46
found % 7.47.

EXAMPLE 13 :

1-(3,3-diphenylpropyl)-4-(3,trifluoromethylphenyl)-4-propionyloxy piperidine and its hydrochloride (II, R = $-O-COC_2H_5$, aryl = )

(code number 71-275 R and C ; preparation according to Scheme G).

In a 100 ml grinded flask equipped with a reflux condenser are introduced 3.5 g (0.008 mol) of the product described in Example 12, 50 ml of anhydrous chloroform and 0.88 ml (0.01 mol) of propionyl chloride. The mixture is heated under reflux for 3 days. The solvent is evaporated and the residue triturated with ether.

3.7 g of the desired salt are obtained (i.e. a yield of 87.3%). It melts at 224°. Its solubility in water is less than 1×10^{-4}%.

Analysis : Ionised Cl calculated % 6.68

found % 6.67.

The products of the invention have been subjected to a pharmacological experimentation programme which has shown their interesting properties, notably their analgesic, spasmolitic and antitussive properties. Among the compounds given as examples, 70-286 R and C and 71-206 R and C have been used in the form of their maleates and the others in the form as their hydrochlorides. The results are expressed in weight of the base.

ACUTE TOXICITY

The tests were carried out on mice of both sexes of Swiss stock, of weight varying between 18-22 g. The 50% lethal doses were calculated according to the method of Miller and Tainter (Proc. Soc. Exp. Biol. Med. 1944, 57, 261).

The results are tabulated in Tables Ia and Ib which likewise indicates the LD_{50} of the comparison substance, the hydrochloride of ethyl 1-(3,cyano-3,3-diphenylpropyl) piperidine carboxylate or diphenoxylate.

SCREENING

The preliminary observations are likewise reported in Tables Ia and Ib.

T A B L E Ia

Products R and C	LD_{50} in mg/kg			Screening
	intraveneous	intraperiteneal	oral	
70-263	-	90	-	At toxic doses, mydriasis and diminution of motor activity.
70-264	-	75	550	At subtoxic doses irritability, analgesia, trembling and convulsions. At toxics doses, Straub's phenomenon.
70-285	43	220	At 500 no mortality in 24 hours	At nontoxic doses, mydriasis, irritability and Straub's phenomenon. Analgesia. At subtoxic doses, exophtalmia, crisis and convulsions. Deaths took place by respiratory arrest.
70-286	-	1200	-	At nontoxic doses, analgesia and mydriasis. At toxic doses, diminution of motor activity and muscular tonus. Straub's phenomenon.

T A B L E Ib

Product R and C	LD_{50} intraperiteneal mg/kg	LD_{50} oral mg/kg	Screening
70-308	>1600	>3000	At nontoxic doses, analgesia and diminution of muscular tonus.
71-119	>1600	>3000	At nontoxic doses, analgesia, motor uncoordination, irritability, diminution of muscular tonus and mydriasis.
71-206	150	>1000	At nontoxic doses, diminution of muscular tonus and motor activity, mydriasis. At toxic dosages, the same + convulsions.
71-254	350	>2000	At nontoxic doses, motor incoordination, trembling, diminution of motor activity. At subtoxic doses, convulsions, mydriasis, diminution of righting reflex.
71-275	1760	2200	At nontoxic doses, analgesia.
71-276	75	240	At nontoxic doses, analgesia, mydriasis, motor uncoordination, trembling, diminution of motor activity and of muscular tonus + Straub's phenomenon.
Comparison product: diphenoxylate	-	500	

Analgesic Activity.

a) Method of 2-phenyl-1,4-benzoquinone.

The procedure of Siegmund et Coll. (Proc. Soc. Exp. Biol. Med. 1957, 95, 729) as modified by Brittain et Coll. (Nature, Lond. 1963, 20, 895) was used.

The intraperitoneal injection of 2-phenyl-1,4-benzoquinone provoked in mice a particular syndrome to which the analgesics were antagonists. The obtained protection was evaluated 20 minutes after the oral administration of the product under study. The reference substances were aminopyrine and dextromoramide.

The Tables IIa and IIb set forth the percentages of diminution of the number of writhing of the animals subjected to treatment.

T A B L E IIa

Products	Oral Dosage mg/kg	Diminution (%) of the number of writhing
70-263 R and C	50	25
idem	100	78
70-264 R and C	25	65
idem	100	100
70-285 R and C	0.187	38
idem	0.375	55
"	0.750	73
70-286 R and C	3	57
idem	6	83
"	12.5	71.7
aminopyrine	50	52
dextromoramide	4	71

T A B L E IIb

Products R and C	Oral Dosage mg/kg	Diminution (%) of the number of writhing
70-308	100	10
71-119	6.25	41
71-206	25	53
71-254	50	32
71-275	12.5	43
71-276	25	58
Comparison substances :		
aminopyrine	50	51
diphenoxylate	7.50	50

b) Heated plate method.

The technique of Boissier (Anesth. Analg. 1956, 13, 569) in mice was used. The results, set forth in Table IIIa for product 70-285 R and C and in Table IIIb for products 71-119 and 71-206 R and C express the percentage increase in the reaction time of the animals.

c) Thermic stimulation of the tail of mice (d'Amour et Smith, J. Pharmacol, Exp. Therap. 1941, 72, 74). The modification of Carron et Coll. was used (Therapie 1952, 7, 27). The results are likewise given in Table IIIa for compounds 70-285 R and C.

TABLE IIIa

Products	Oral Doses mg/kg	Increase (%) of reaction time at the end of			
		30 min.		90 min.	
		heated plate	mouse tail	heated plate	mouse tail
70-285 R and C	0.5	30	-	0	-
idem	1	62	-	30	-
aminopyrine	150	78	-	60	-
pentazocine	50	<10	-	<10	-
dextromoramide	5	87	-	75	-
70-285 R and C	2	-	25	-	0
idem	5	-	100	-	25
dextromoramide	5	-	25	-	0
idem	10	-	50	-	12

TABLE IIIb

Product R and C	Oral Doses mg/kg	Increase (%) of reaction time at the end of	
		30 minutes	90 minutes
71-119	50	42	64
71-206	75	17	18
Comparison substance: aminopyrine	150	75	62

d) Stimulation of rabbit tooth.

The experimental procedure of Laffargue (doctoral thesis of Paris University, distinction in pharmacy, undertaken 10.6.63 : Contribution to the use of electric stimulation on the dental pulp of the rabbit for the study of antipyretic analgesics), was used.

Table IIIc expresses the results as a percentage of the increase in threshhold voltage for compound 70-285 R and C, and the reference product (aminopyrine).

TABLE IIIc

Products	Dose intraveneous mg/kg	Augmentation (%) of the threshhold voltage at the end of										
		5 mn	10 mn	15 mn	20 mn	25 mn	30 mn	35mn	40 mn	45 mn	50 mn	55 mn
70-285 R & C	0,330	jaws contracted	jaws contracted	jaws contracted	66	108	125	91	75	58	33	8
Aminopyrine	50	0	10	40	50	65	65	50	35	10	5	0

Respiratory Activity.

a) The respiration of a non-depressed rabbit was recorded for 70-285 R and C by means of the insertion into the trachea of a canula provided with a Marey capsule ; 75 mg/kg (intraveneous) of 70-285 R and C had the same depressive activity as 15 mg/kg of dextromoramide injected in the same fashion.

b) Compounds 71-119, 206, 275 and 276.

A mouse, treated intraperitonealy by one of the products under study, was placed in a hermetic enclosure and the variations in pressure induced by the respiratory movements of the mouse were registered by means of a low pressure Statham cell connected to a Schwartzer polygraph. Measurements were started 5 minutes after the injection and the number of respiratory movements recorded in periods of 5 seconds obtained from the trace. The results are expressed in a percentage depression of respiration, in comparison to that given by the reference substance, the diphenoxylate. The results are set forth in Table IV.

T A B L E IV

Products R and C	dose mg/kg intraperitoneal	respiratory depression %
71-119	25	46
71-206	25	46
71-275	25	32
71-276	25	45
reference substance : diphenoxylate	6.25	65

A1

Activity on the intestinal transit.

a) According to the technique of Janssen and Jageneau (J. Pharm. Pharmacol. 1957, 9, 381) using the study of intestinal transit of a carbon meal in mice, it was observed that 1mg/kg of 70-285 R and C administered intraperitonealy had the same retardent action as 5 mg/kg of dextromoramide or 80 mg/kg of codeine phosphate injected in the same fashion.

b) For other compounds the method of Macht (J. Am. Pharm. Assoc. 1931, 20, 550) was used allowing the study of the intestinal transit of a carbon meal in mice and the results were compared with those which were observed with the reference substance, the diphenoxylate.

The results are set forth in Table V. They are expressed in a percentage inhibition of the speed of intestinal transit.

T A B L E V

Products R and C	Oral dose mg/kg	% inhibition
70-308	300	50
71-119	15	38
71-206	15	40
71-254	60	48
71-275	15	41
71-276	15	53
Comparison substance : diphenoxylate	15	50

Antitussive effect.

The antitussive effect was studied in guinea pigs

subjected to a citric acid aerosol according to the experimental procedure of Tiffeneau, (Therapie, 1956, 11, 265) modified by Charlier and Prost (Arch. Int. Pharmacodyn. 1961, 134, No. 3/4).

The reference substance was codeine phosphate.

The results, expressed in Table VI, are expressed as a percentage of the diminution of the number of attacks of coughing.

T A B L E VI

Products R and C	dose intraperitoneal mg/kg	% diminution of the number of coughing fits
70-308	1	63
71-119	1	46
71-206	1	45
71-254	1	37
71-275	1	50
Comparison substance : codeine phosphate	15	37

Following the preceding results it can be seen that the products of the invention possess analgesic spasmolytic and/or antitussive activity. In particular, compound 70-285 R and C is an analgesic which exercises an activity 2 to 5 times stronger than that of dextromoramide with a respiratory depressant effective 5 times weaker.

Compound 71-119 R and C has shown itself to be an analgesic 3 to 7 times stronger than aminopyrine ; compounds 71-119, 71-206, 71-275 R and C have a spasmolytic activity comparable to that of diphenoxylate for a toxicity much weaker : all the tested compounds have an antitussive activity

very superior to that of codeine. Furthermore they provoke a respiratory depression much less than that of diphenoxylate.

According to their characteristics, these compounds can thus be used in human and veterinary therapy for the treatment of algesiae (cephaleas post operative pains, hepatic or nephretic colics, etc.) for the premidication of processes with a view to diagnosis, cares or surgical operations, for the treatment of acute and chronic diarrhoeas, where they are of infectious, parasitic or alimentary origin, and finally for the treatment of spasmodic or irratative coughs, tracheitis and coughs accompanying infections of the respiratory system.

The method of administration can be oral, rectal, or parenteral (in particular subcutaneous and intramuscular) for compounds of Examples I to 7, particular the compounds of 70-285, 70-286, 70-263 and 70-264 ; it may be oral for the compounds of examples 8 to 13, particularly compounds 71-119, 70-308, 71-206, 71-254, 71-275 and 71-276.

For oral administration can be used tablets, dragees, drinkable ampoules, etc., for rectal administration suppositaries, and for parenteral administration injectable solutions, in association with the usual excipients for this type of medicament.

The posology should be as follows :

a) 70-285 R and C : orally, dose per unit taken 0.2 to 5.0 mg, the maximum daily dose being 50 mg ; rectally, these quantities are respectively 0.2 to 10 mg and 100 mg ; parenterally they are 0.1 to 5 mg and 25 mg respectively.

b) 70-286 R and C : orally, dose per unit taken 1 to 50 mg, daily maximum dose being 0.5 g ; rectally the quantities are respectively 1 to 100 mg and 1 g ; parenterally they are 0.5 to 50 mg and 250 mg respectively.

c) 70-263 R and C and 70-264 R and C : orally, dose per unit taken 20 to 500 mg, daily maximum dose being 2g ; rectally these quantities are respectively 20 to 1000 mg and 3 g ; parenterally they are 5 to 100 mg and 500 mg.

d) compounds of 71-119, 70-308, 71-206, 71-254, 71-275 and 71-276 R and C : orally, dose per unit taken 1 to 100 mg, the daily maximum dose being 0.5 g ; rectally, quantities respectively 1 to 200 mg and 1 g.

The non-limitative examples which follow show pharmaceutical forms :

Tablets.

Hydrochloride of 71-119 R and C 2.5 mg

Excipient as necessary to make 1 tablet of 20 mg

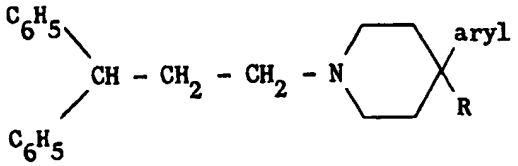
Suppositories.

Hydrochloride of 70-308 R and C 10 mg

Immhausen's Excipient as necessary to make 1 adult suppository.

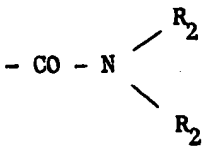
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the preparation of a compound of the formula:



(I)

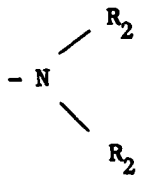
in which aryl represents a phenyl or m-trifluoromethylphenyl group and R represents a group selected from hydroxyl; - O - COR_1; - CH_2OH, - CH_2 - O - COR_1; - COR_1; - CN;



or

- O - CO - OR_1; provided that when aryl represents an m-trifluoromethylphenyl group, R must represent hydroxyl or - O - COR_1;

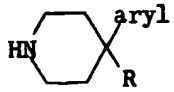
in which groups R_1 represents an alkyl group containing from 1 to 4 carbon atoms, and R_2 represents a hydrogen atom, a methyl or ethyl group or



represents a pyrrolidine ring;

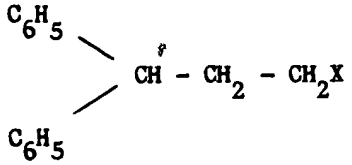
or a pharmaceutically acceptable salt thereof, the process being selected from

a) reacting the compound of the formula III



(III)

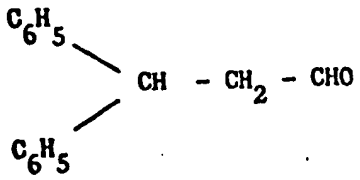
in which aryl and R are as defined above with a compound of the formula (IV);



(IV)

in which X is a halogen atom;

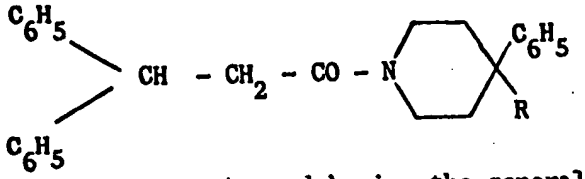
b) reacting together under reducing conditions an aldehyde of the formula



(V)

with a compound having the general formula III as defined above;

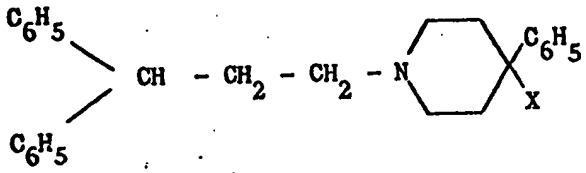
c) reducing a compound having the general formula VI



(VI)

d) esterifying a compound having the general formula I above but in which R only represents hydroxyl or hydroxy methyl with a carboxylic acid having the formula R_1 COOH or the anhydride or a halide of such an acid;

e) hydrolyzing a compound having the formula VIII



(VIII)

in which X is a halogen;

and, in all cases, when a pharmaceutically acceptable salt is required converting the product into the required salt.

2. A process as claimed in claim 1 for preparing 1-(3,3-diphenyl-1-propyl)-4-phenyl-4-piperidinol and its pharmaceutically acceptable salts that comprises reacting 4-phenyl-4-piperidinol with 1-bromo-3,3-diphenyl-propane and, if the free base be required, converting the hydrobromide thus obtained into the free base or into another pharmaceutically acceptable salt or converting the obtained free base into a pharmaceutically acceptable salt.

3. A process as claimed in claim 1 for preparing 1-(3,3-diphenyl-1-propyl)-4-phenyl-4-piperidinol and its pharmaceutically acceptable salts that comprises reacting 4-phenyl-4-piperidinol with 3,3-diphenylpropionaldehyde under catalytically reducing conditions and, if a salt be required, converting

the product into a pharmaceutically acceptable salt.

4. A process as claimed in claim 1 for preparing 1-(3,3-diphenyl-propyl) -4-phenyl-4-piperidinol or its pharmaceutically acceptable salts that comprises hydrolyzing 1-(3,3-diphenyl-1-propyl)-4-phenyl-4-bromopiperidine and, if a salt be required, converting the product into a pharmaceutically acceptable salt.

5. A process as claimed in claim 1 for preparing 1-(3,3-diphenyl-1-propyl)-4-phenyl-4-propionyloxy piperidine or its pharmaceutically acceptable salts that comprises esterifying 1-(3,3-diphenyl-1-propyl)-4-phenyl-4-piperidinol with propionyl chloride and, if a salt be required, converting the product into a pharmaceutically acceptable salt.

6. A process as claimed in claim 1 for preparing 1-(3,3-diphenyl-1-propyl)-4-phenyl-4-hydroxymethyl piperidine or its pharmaceutically acceptable salts that comprises reacting 4-phenyl-4-hydroxymethyl piperidine with 1-bromo-3,3-diphenylpropane and, if a salt be required, converting the product into a pharmaceutically acceptable salt.

7. A process as claimed in claim 1 for preparing 1-(3,3-diphenyl-1-propyl)-4-hydroxymethyl piperidine or its pharmaceutically acceptable salts that comprises producing 1-(3,3-diphenylpropionyl)-4-phenyl-4-ethoxy-carbonyl-piperidine and, if a salt be required, converting the product into a pharmaceutically acceptable salt.

8. A process as claimed in claim 1 for preparing 1-(3,3-diphenyl-1-propyl)-4-phenyl-4-propionyl piperidine or its pharmaceutically acceptable salts that comprises reacting 4-phenyl-4-propionyl piperidine with 1-bromo-3,3-diphenylpropane and, if the free base be required, converting the hydrobromide thus obtained into the free base or into another pharmaceutically acceptable salt or converting the obtained free base into a pharmaceutically acceptable salt.

9. A process as claimed in claim 1 for preparing 1-(3,3-diphenylpropyl)-

4-phenyl-4-cyanopiperidine or its pharmaceutically acceptable salts that comprises reacting 4-phenyl-4-piperidino nitrile with 3,3-diphenylpropyl bromide and, if the free base be required, converting the hydrobromide thus obtained into the free base or into another pharmaceutically acceptable salt or converting the obtained free base into a pharmaceutically acceptable salt.

10. A process as claimed in claim 1 for preparing 1-(3,3-diphenylpropyl)-4-ethoxycarbonyloxy-4-phenylpiperidine or its pharmaceutically acceptable salts that comprises esterifying 1-(3,3-diphenylpropyl)-4-phenyl-4-piperidinol with ethychloroformate and, if a salt be required, converting the product into a pharmaceutically acceptable salt.

11. A process as claimed in claim 1 for preparing 1-(3,3-diphenylpropyl)-4-phenyl-4-pyrrolidino carboxyamido piperidinee or its pharmaceutically acceptable salts that comprises reacting 1-(3,3-diphenylpropyl)-4-phenyl piperidine-4-carboxylic acid chloride with pyrrolidine and, if the free base be required, converting the produced hydrochloride into the free base which, in turn, may be be converted into a pharmaceutically acceptable salt.

12. A process as claimed in claim 1 for preparing 1-(3,3-diphenylpropyl)-4-phenyl-4-carboxamido piperidine or its pharmaceutically acceptable salts that comprises reacting 1-(3,3-diphenylpropyl)-4-phenyl piperidine-4-carboxylic chloride with ammonia and, if the free base be required, converting the produced hydrochloride into the free base which, in turn, may be converted into a pharmaceutically acceptable salt.

13. A process as claimed in claim 1 for preparing 1-(3,3-diphenylpropyl)-4-(3,trifluoromethylphenyl)-4-piperidinol that comprises reacting 4-(3,trifluoromethylphenyl)-4-piperidinol with 3,3-diphenylpropylbromide and, if the free base be required, converting the hydrobromide thus obtained into the free base or into another pharmaceutically acceptable salt or converting the

the obtained free base into a pharmaceutically acceptable salt.

14. A process as claimed in claim 1 for preparing 1-(3,3-diphenylpropyl)-4-(3,trifluoromethylphenyl)-4-propionyloxy piperidine or its pharmaceutically acceptable salts that comprises reacting 1-(3,3-diphenylpropyl)-4-(3,trifluoromethylphenyl)-4-piperidinol with propionyl chloride and, if the free base be required, converting the resulting hydrochloride into the free base which, in turn, may be converted into a pharmaceutically acceptable salt.